# Writing the Development Safety Update Report (E2F): What You Need to Know

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# Overview

- Background
- Differences between DSUR and US IND annual report
- What that means for DSUR outsourcing and production
- Why DSUR medical writers must function as project managers
- Tips for success



# Background

- ICH meeting in Yokohoma, June 2009, discussed DSUR but didn't reach Step 4
- Step 4 "is expected in autumn 2009"
- US IND annual reports (i.e., safety reports covering clinical trials) have been required for far longer than in the EU or Japan, yet corresponding US regulations are very brief (3/4 of a page: 21 CFR 312.33)

## Background (2)

- Draft DSUR (E2F Step 2, June 2008) guideline, 27 pages; E2F WG received 70 pages of industry comments about it
- EU Annual Safety Report corresponding to US IND annual report: implemented May 2004
- Japanese periodic report implemented in 2009



## DSUR vs. US IND Annual Report

- DSUR combines pre-marketing safety report requirements in Europe, Japan, and US; intended to mirror PSUR (strong future possibility of integration)
- DSUR structure and differences from US IND Annual Report
- What FDA wants in the DSUR and suggestions for achieving this

# DSUR Structure (not final!)

Executive Summary

1. Introduction *(be brief!)*
2. Worldwide Marketing Authoris/zation Status
3. Update on Actions Taken in the Reporting Period for Safety Reasons
   - *Includes new concept: "regulatory constraints on development"*



# Regulatory Constraints…?

- "Regulatory authority advice given for safety reasons involving a constraint on development, i.e.,
  - Requirement to provide data from a specific, long-term animal study prior to initiating repeat dosing in humans
  - Development of an acceptable immunogenicity assay prior to Phase III"

## Regulatory Constraints…? (2)

- "Standard requirements (ICH and other) should not be included in the list, e.g., a thorough QT study
- Include a cumulative list of this advice as a table in the appendix"

*-Per Dr. Ellis Unger, FDA, E2F Working Group Rapporteur, at the June 2009 DIA annual meeting*



## DSUR Structure

4. Changes to Reference Safety Information
5. Brief overview of clinical trials ongoing and completed during reporting period
6. Estimated Exposure
   - 6.1 Cumulative exposure in clinical trials (Phase I – IV)
   - 6.2 Exposure from marketed setting

# DSUR Structure

7. Presentation of Safety Data from Clinical Trials *(in the reporting period)*
   - 7.1 General Considerations
   - 7.2 Interval line listings of SARs *(to meet EU needs)*
   - 7.3 Cumulative SAE tabulations *(to meet US needs)*
   - 7.4 Deaths
   - 7.5 Drop outs associated with any AE



# DSUR Structure

8. Significant Findings from Clinical Trials During the Reporting Period
   - 8.1 Completed trials/interim analyses
   - 8.2 Ongoing clinical trials
   - 8.3 Other therapeutic use of investigational drug
   - 8.4 New safety data related to combination therapies

# DSUR Structure

9. Relevant Findings from Noninterventional Studies
10. Relevant Findings from Other Studies
11. Safety Findings from Marketing Experience
12. Other Information
    - 12.1 Non-clinical data
    - 12.2 Long-term follow up



# DSUR Structure

12. Other Information (continued)
    - 12.3 Literature
    - 12.4 Other DSURs
    - 12.5 Significant manufacturing changes
    - 12.6 Lack of efficacy
    - 12.7 Phase I protocol modifications
    - 12.8 Plan for coming year *(not found in step 2)*

# DSUR Structure

13. Late-Breaking Information
14. Overall Safety Information
    - 14.1 Evaluation of the risks
    - 14.2 Benefit-risk considerations
    - 14.3 Conclusions
15. Summary of important risks

Appendices



# Differences from IND Annual Report

- One DSUR for one investigational drug, due within 60 days after the date of first Clinical Trial Application “ok to proceed” in any region, and not longer than 60 days after the data lock point
- Single data lock point: last day of the 1 year reporting period, or last day of month prior to Day 1 of birth date month

# One DSUR for One Product?

Yes, one DSUR for all of the product's indications, formulations, and routes of administration

But, if one DSUR does not make sense scientifically, two can be submitted *(discuss with the regulatory authority)*



# What FDA Wants in a DSUR

- DSUR should not be a "data dump"
- To see if risks are managed appropriately
- To see if assessment of the product's risk has changed, and if so, has the development program changed to address it?
- Clear conclusions

# DSUR Considerations

- Executive Summary (not part of US IND Annual Report) is submitted to Ethics Committees, whereas IND Annual Report is proprietary, **not** distributed outside FDA
- Section 3: provide cumulative list of unique requirements from Authorities
- Sections 5 – 7: do not provide commentary, put data in appendices



# DSUR Considerations

- Sections 8 – 11: discuss what was learned about safety of the product in the last year
- Section 12: discuss the findings
- Section 14: make it concise, how was risk managed, what were actions and changes
- Section 15: potential issues to address, "*very important to FDA*"

# DSURs for FDA

- The IND annual report will continue to be accepted by FDA even after the DSUR is Step 4
- The E2F WG were careful to craft the DSUR so that it does meet all US and EU safety requirements for premarketing safety reports



# DSUR Outsourcing?

- Ensure contract writer understands DSUR structure **and intent**
- Ensure contract writer understands how to report and discuss adverse event categories and data appropriately
- Allow additional time to write and review DSUR (new format for everyone!)

## Medical Writer as Project Manager

- Imperative for medical writer to ensure the DSUR is concise and appropriate (not a data dump!)
- Ensure data are organized logically (new concept for US that DSUR covers all indications, routes, formulations)
- Work closely with Safety and Regulatory Groups to ensure success



## Sources:

- Ellis Unger, FDA
- Val Simmons, Eli Lilly
- Yukiko Watabe, Chugai
- 21 CFR 312.33
- www.ich.org (e2f)
- www.fda.gov

# Abbreviations and Terms

CFR = *(US)* Code of Federal Regulations

DSUR = Development Safety Update Report *(Pre-marketing)*

ICH = International Conference on Harmonis/ zation

IND = *(US)* Investigational New Drug Application

PSUR = Periodic Safety Update Report *(Post-marketing)*

WG = working group



# Questions about the presentation?

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